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(54) Title: USE OF MAS-COMPOUNDS FOR TREATING DISEASES ASSOCIATED WITH LIPID METABOLISM

(57) Abstract: Certain sterols can be used for increasing the HDL cholesterol to non-HDL cholesterol ratio, for treatment and/or prevention of artherosclerosis, for treatment and/or prevention of hyper-lipidemia, for treatment of diabetic dyslipididemia, for treatment of hyper-cholesterolemia, for treatment of diseases of illness related to metabolic dysfunction, for treatment of obesity or obesitas related diseases, and for the treatment of neurological diseases.

USE OF MAS-COMPOUNDS FOR TREATING DISEASES ASSOCIATED WITH LIPID METABOLISM

FIELD OF THE INVENTION

This invention relates to the use of novel compounds mentioned below for increasing the HDL cholesterol to non-HDL cholesterol ratio, for treatment and/or prevention of atherosclerosis, for treatment and/or prevention of hyperlipidemia, for treatment of diabetic dyslipididemia, for treatment of hyper-cholesterolemia, for treatment of diseases of illness related to metabolic dysfunction, for treatment of obesity or obesitas related diseases, and for treatment of neurological diseases, for example, Alzheimer, associated with lipid metabolism. The present invention also embraces pharmaceutical compositions and kits comprising these compounds and methods of using the compounds and their pharmaceutical compositions, for example, to humans.

BACKGROUND OF THE INVENTION

Herein the term lipoprotein covers any of the lipid-protein complexes in which lipids are transported in the blood. Lipoprotein particles consists of a spherical hydrophobic core of triglycerides or cholesteryl esters surrounded by an amphiphatic monolayer of phospholipids, cholesterol, and apolipoproteins. The expression HDL cholesterol covers high-density lipoprotein and the expression non-HDL cholesterol covers the remaining lipoproteins.

Atherosclerosis is an extremely common form of arteriosclerosis in which deposits of yellowish plaques (atheromas) containing cholesterol, lipid material, and lipophages are formed within the intima and inner media of large and medium-sized arteries. Arterosclerosis is a group of diseases characterized in thickening and loss of elasticity of arterial walls.

Hyperlipidemia is a general term for elevated concentrations of any or all of the lipids in the plasma, including, for example, hypertriglyceridema and hypercholesterolemia.

Diabetic dyslipidemia is the typical lipid disorder associated to type II diabetes characterized by low HDC, high LDC, and high small very dense lipid particles.

Hyper-cholesterolemia is the presence of an excess of cholesterol in the blood.

Metabolic dysfunctions cover the general term describing an inappropriate regulation of the glucose and lipid metabolism.

Alzheimer's disease is a progressive degenerative disease of the brain of unknown etiology characterized by diffuse atrophy throughout the cerebral cortex with distinctive histopathology changes termed "senile plaques" (microscopic lesions composed of fragmented

axon terminals and dendrites surrounding a core of amyloidal) and "neurofibrillary tangles" (intracellular knots or clums of neurofibrils).

In many countries, obesity is becoming a steadily increasing problem. Great effort has been devoted to this problem and the elevated health risk associated with obesity and metabolic imbalance. For example, over weighty people have an increased risk of developing diabetes. For several subgroups of the population, for example, diabetics, overweight increases the risks in connection with the parent disease. Recent research also revealed connections between cholesterol metabolism and diseases of the central nervous system. For example, it is possible to delaying or preventing the onset of Alzheimer disease by cholesterol synthesis inhibitors. Large portions of the health care budgets are nowadays used in obesity or obesity related fields.

Many steps in the cholesterol synthesis are known. For example, the cholesterol synthesis proceeds via the following compounds: HMG-CoA → evalonic acid → lanosterol → FF-MAS → T-MAS → desmosterol → cholesterol. Several statins, for example, Simvastatin, are known to interact on the HMG-CoA → evalonic acid step. The desmosterol → cholesterol is controlled by a sterol Δ^{24} reductase.

One object of this invention is to provide a medicament which can be used for increasing the HDL cholesterol to non-HDL cholesterol ratio.

Another object of this invention is to provide a medicament which can be used for treatment and/or prevention of artherosclerosis.

A further object of this invention is to provide a medicament which can be used for treatment and/or prevention of hyperlipidemia.

A still further object of this invention is to provide a medicament which can be used for treatment of diabetic dyslipididemia.

A still further object of this invention is to provide a medicament which can be used for treatment of hyper-cholesterolemia.

A still further object of this invention is to provide a medicament which can be used for treatment of diseases of illness related to metabolic dysfunction.

A still further object of this invention is to provide a medicament which can be used for treatment of obesity or obesitas related diseases.

A still further object of this invention is to provide a medicament which can be used for treatment of neurological diseases, e. g. Alzheimer disease.

Other objects of the present invention will become apparent upon reading the present description.

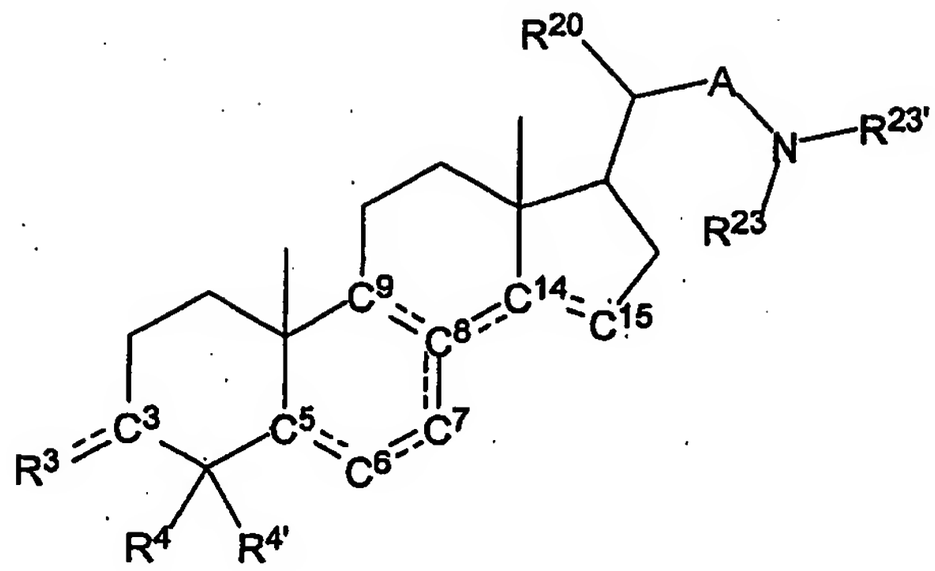
DEFINITIONS

Herein, FF-MAS is 4,4-dimethyl-5α-cholesta-8,14,24-triene-3β-ol, T-MAS is 4,4-dimethyl-5α-cholesta-8,24-diene-3β-ol (also designated 4,4-dimethylzymosterol), and ZK 255884 is (20S)-20-[(piperidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol (compound No. 2 in the list below).

DESCRIPTION OF THE INVENTION

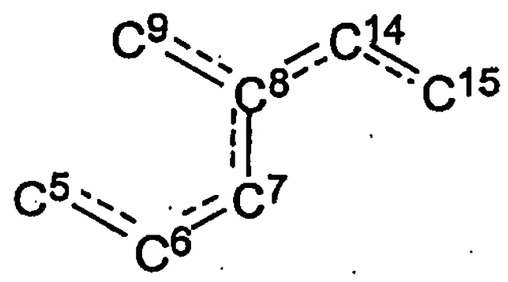
It has now, surprisingly been found that certain compounds hereinafter designated MAS compound which are defined below can be used for increasing the HDL cholesterol to non-HDL cholesterol ratio, for treatment and/or prevention of artherosclerosis, for treatment and/or prevention of hyperlipidemia, for treatment of diabetic dyslipididemia, for treatment of hyper-cholesterolemia, for treatment of diseases of illness related to metabolic dysfunction, and for treatment of obesity or obesitas related diseases.

Herein MAS compounds are all compounds of the general formula I, Ia, Ib, and Ic mentioned in any of the international patent applications having the international publication number WO 96/00235 (our ref.: 4228), WO 97/00884 (our ref.: 4475), WO 98/28323 (our ref.: 5141), WO 99/32506 (earliest priority: 971218), WO 98/52965 (earliest priority: 970516), WO 99/67273 (our ref.: 5558), WO 99/58549 (our ref.: 5509), or WO 2000/47604 (our ref.: 5769), WO 2000/68245 (our ref.: 6238), or WO 2001/62771 (our ref.: 6239), preferably all the specific compounds mentioned specifically in said WO specifications covered by said formula, as well as compounds of the general formula X shown below:



X

wherein in the moiety of the following formula



XA

each bond between C^5 and C^6, between C^6 and C^7, between C^7 and C^8, between C^8 and C^9, between C^8 and C^{14} and between C^{14} and C^{15}, independently, is a single bond or a double bond, at least one of these bonds being a double bond, and wherein each carbon atom C^5, C^6, C^7, C^8, C^9, C^{14} and C^{15} is bonded to each neighbouring C atom by a single bond or at the most by one double bond, and wherein between all other carbon atoms of the steroid skeleton are single bonds, and C^3R^3 is a) C^3=O or b) C^3H-O$R^{3'}$, wherein $R^{3'}$ is selected from the group, comprising hydrogen, unsubstituted or substituted, linear or branched C_1 - C_{10} alkyl and C^3(O)-$R^{3''}$, bonded to the CH-O moiety via the C(O) moiety, wherein $R^{3''}$ is selected from the group, comprising i) substituted or unsubstituted, linear or branched C_1 - C_{10} alkyl, ii) substituted or unsubstituted, linear or branched C_1 - C_{10} fluoro alkyl, iii) unsubstituted or substituted C_6 - C_{10} aryl, iv) unsubstituted or substituted C_5 - C_{10} heteroaryl, v) unsubstituted or substituted, linear or branched C_1 - C_{10} alkyloxy and vi) unsubstituted or substituted, linear or branched C_1 - C_{10} alkylamino, or c) C^3H-SO_2-$R^{3''}$ or C^3=NO$R^{3''}$, wherein $R^{3''}$ has the same meaning as above, or d) C^3H-O-$R^{3'''}$, wherein $R^{3'''}$ is unsubstituted or substituted, linear or branched C_2 - C_{10} alkylen and forms a cyclic ether both with the C atom of the steroid skeleton and the O atom, or e) a cyclic ring structure with the C^3 atom, wherein R^3 is unsubstituted or substituted, linear or branched C_2 - C_{10} alkylen, or f) C^3H-Hal, wherein Hal is F, Cl, Br or I,

and R^4, $R^{4'}$ and R^{20}, independently, are selected from the group, comprising hydrogen and unsubstituted or substituted, linear or branched C_1 - C_4 alkyl, and R^{23} and $R^{23'}$, independently, are selected from the group, comprising: a) hydrogen, b) unsubstituted or substituted, linear or branched C_1 - C_8 alkyl, c) unsubstituted or substituted, linear or branched C_2 - C_8 alkenyl, d) unsubstituted or substituted, linear or branched C_1 - C_8 alkyl, at least one of the alkyl carbon atoms being substituted by any of O, N and S, e) unsubstituted or substituted, linear or branched C_2 - C_8 alkenyl, at least one of the alkenyl carbon atoms being substituted by any of O, N and S and f) unsubstituted or substituted, linear or branched C_6 - C_{10} aryl, or R^{23} and $R^{23'}$ together form a) an unsubstituted or substituted, linear or branched C_2 - C_7 alkylen, especially C_5 - C_7, group or b) an unsubstituted or substituted, linear or branched C_2 - C_7 alkylen, especially C_5 - C_7, group, wherein at least one of the alkylen carbon atoms is replaced by any of O, N and S, and A is a methylen or ethylen group, the group being unsubstituted or substituted methylen or ethylen; in a preferred embodiment of the present invention A is methylen or ethylen.

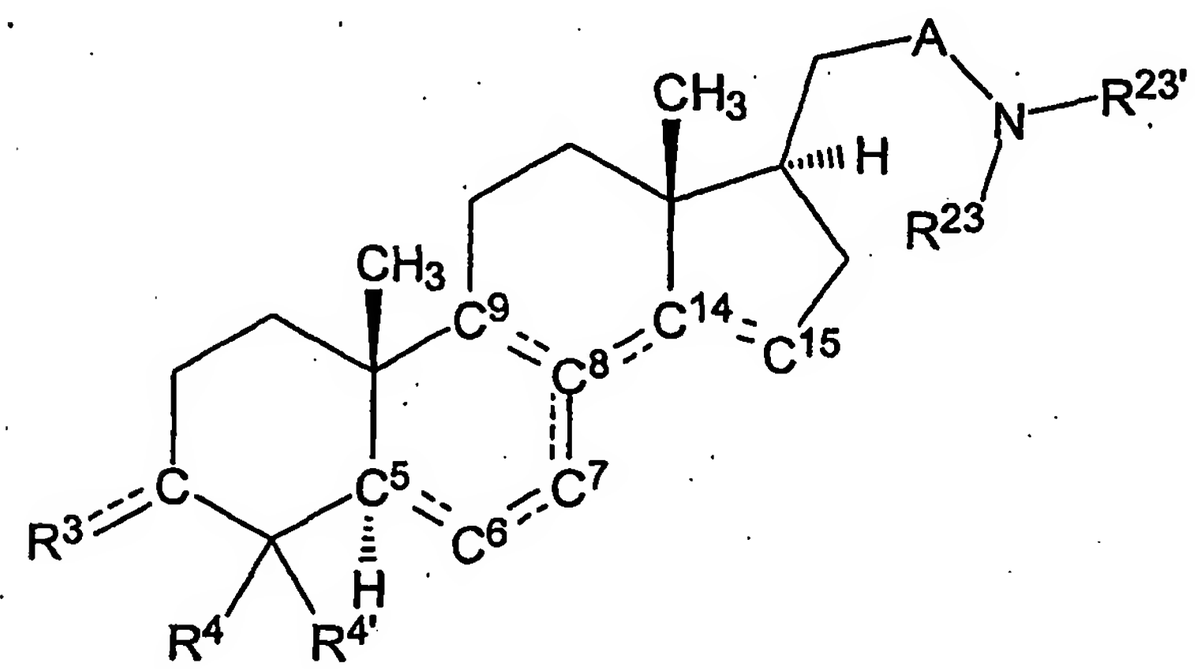
The content of the above WO specifications is hereby incorporated by reference.

Preferred compounds of formula X are such in which at least one double bond is present in the steroid skeleton between carbon atoms C^6, C^7, C^8, C^9, C^{14} and C^{15}, respectively. In one further preferred embodiment of this invention, a double bond may be present between C^5 und C^6 in addition to the at least one double bond between C^6, C^7, C^8, C^9, C^{14} and C^{15}, respectively. It is especially preferred to have a sterold in which the double bonds are conjugated to each other if more than one double bond is present in the steroid skeleton.

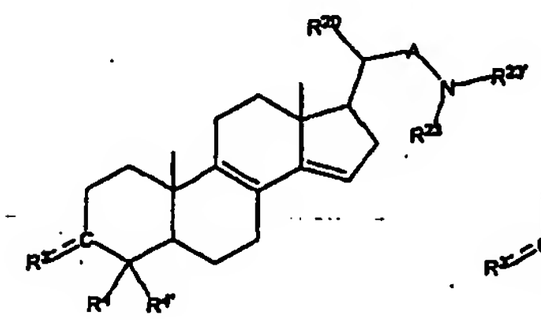
All indications to C_n alkyl, C_n fluoroalkyl, C_n alkyloxy, C_n alkylamino, C_n cycloalkyl, C_n alkylen, C_n alkenyl, C_n aryl, C_n heteroaryl and the like relate to radicals with n carbon atoms in the molety, the number of n carbon atoms including all carbon atoms in side chains of for example, branched radicals. Unless otherwise described herein, an alkyl, alkoxy, alkylen or acyl group has 1 to 10 carbon atoms including side chain carbon atoms if these groups are branched; an alkenyl or alkynyl group has 2 to 10 carbon atoms including side chain carbon atoms if these groups are branched; further a cycloalkyl has 4 to 7 carbon atoms; an aryl has 6 to 10 carbon atoms; and a heterocyclic ring or a heteroaryl have 6 to 10 ring atoms. Further aryl also represents alkylaryl; heteroaryl also represents alkylheteroaryl; and cycloalkyl also represents alkylcycloalkyl.

The novel steroid compounds of formula X have a number of chiral centers such that these compounds exist in several isomeric forms. All these isomeric forms are within the scope of the present invention unless otherwise described herein.

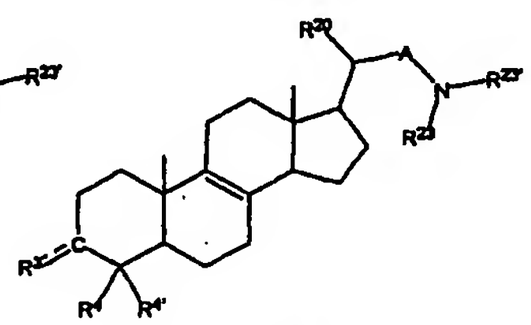
A steroid compound with the general formula below is preferred:



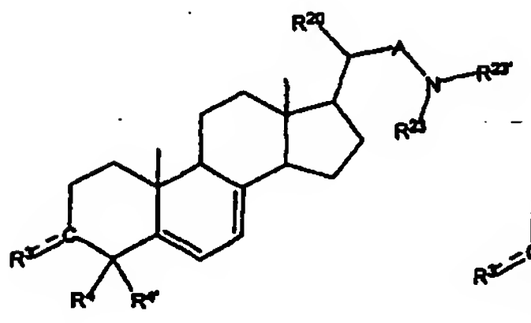
Especially the Δ^5-pregenene derivatives, the $\Delta^{8,14}$-pregnadien derivatives, the Δ^8-pregnene derivatives and the $\Delta^{5,7}$-pregnadiene derivatives are useful as pharmaceutically active steroid compounds, i.e. compounds having the general formulae shown below:



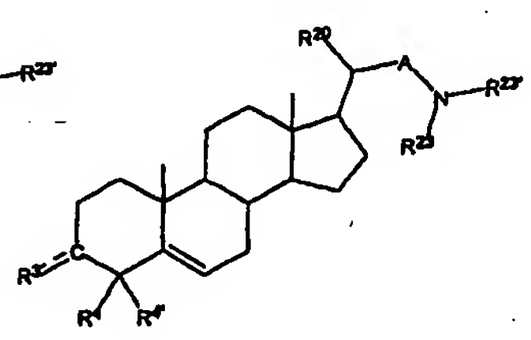
XB'



XB''



XB'''



XB''''

The outstanding properties of the novel compounds may be attributed to the amino group in the side chain linked to the C^{17} carbon atom in the steroid skeleton via a C_2 - C_3 alkylen spacer (including the C^{20}-R^{20} group).

Especially preferred are compounds, wherein the moiety C^3R^3 is CH-OH, in particular a 3β-hydroxy radical bonded to the C^3 atom of the steroid skeleton. The moiety may also be CH-O-C(O)-$R^{3'}$ (= CH-O-$R^{3'}$, wherein $R^{3'}$ is C(O)-$R^{3''}$), wherein $R^{3''}$ is defined as before. In particular R^3 may be an ester radical of a monocarboxylic acid, of a dicarboxylic acid, of an inorganic acid or of any other acid, bonded to the C^3 atom of the steroid skeleton. Especially for R^3 being an ester radical of a dicarboxylic acid $R^{3''}$ may be $(CH_2)_n$-COOH, wherein n = 1, 2, 3, 4, 5 or 6. The ester radical may also be formed from an inorganic acid such as phosphoric acid, sulfuric acid and sulphamic acid, further from a monocarboxylic acid such as acetic acid, propionic acid, *n*-butanoic acid, pivalic acid, benzoic acid, nicotinic acid and isonicotinic acid. In particular the ester radical may be formed from a dicarboxylic acid, such as from succinic acid and glutaric acid.

Further steroid compounds according to the present invention may also include derivatives, in which C-O-R^3 represents a cyclic ether including the C^3 atom of the steroid skeleton.

R^3 may also form a cyclic ring structure together with the C^3 atom, R^3 being unsubstituted or substituted, linear or branched C_2 - C_{10} alkylen. For example, C^3R^3 may be a cyclopropylen, cyclobutylen, cyclopentylen or cyclohexylen radical. It may also represent an unsaturated cyclic ring structure such as cyclopropenylen, cyclobutenylen, cyclopentenylen and cyclohexenylen. The ring structure may also be substituted by any of halogen, hydroxy, alkoxy, aryloxy and the like.

Substances according to the present invention may advantangeously also be compounds, in which $R^{3''}$ is selected from the group comprising fluoromethyl, aryl, heteroaryl and $(CH_2)_n$-COOH, wherein n = 1, 2, 3, 4, 5 or 6, especially compounds, in which $R^{3'}$ (= C(O)-$R^{3''}$) is acetyl, propionyl, pivaloyl, butanoyl, benzoyl, nicotinyl, isonicotinyl, hemi glutaroyl, butylcarbamoyl, phenylcarbamoyl, ethoxycarbonyl and *tert*-butoxycarbonyl. In a particularly preferred steroid compound $R^{3'}$ may be hemi succinoyl.

Further in the novel steroid compounds R^4 and $R^{4'}$, independently, are preferably hydrogen or a linear or branched C_1 - C_4 alkyl group, i.e. methyl, ethyl, propyl and butyl, and especially methyl.

Further R^4 and $R^{4'}$, independently, may also be C_1 - C_4 alkyl, substituted by halogen, hydroxy, alkoxy or aryloxy.

R^{20} is preferably hydrogen or linear or branched C_1 - C_4 alkyl, i.e. methyl, ethyl, propyl and butyl. R^{20} is especially methyl.

R^{23} and $R^{23'}$, independently, may specifically be hydrogen or a C_1 - C_8 alkyl group, such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *tert*-pentyl, *neo*-pentyl, further hexyl and cyclohexyl and the like. Further R^{23} and $R^{23'}$, independently, may also be a C_2 - C_8 alkenyl group, i.e. an unsaturated alkyl group, for example, vinyl, allyl, *iso*-propenyl and prenyl, further C_6 - C_{10} aryl, such as phenyl and 1-naphthyl, this group also comprising alkylaryl, being bonded via the aryl moiety or via the alkyl moiety to the nitrogen atom, for example, benzyl and tolyl. R^{23} and $R^{23'}$ may preferably be alkyl and alkenyl, being substituted by at least one radical, selected from the group, comprising linear or branched C_1 - C_4 alkyl and C_1 - C_4 alkoxy. The phenyl and 1-naphthyl radical may also be substituted by halogen, C_1 - C_4 alkoxy, hydroxy or C_1 - C_4 alkyl, including the fluoroalkoxy and fluoroalkyl derivatives. Further R^{23} and $R^{23'}$, independently, may further be for example, 4-hydroxyphenyl, 4-methoxyphenyl, 2,4,6-trimethylphenyl, 2,4-dichlorophenyl, 4-fluorophenyl, 4-trifluoromethylphenyl and 2-pentafluoroethylphenyl.

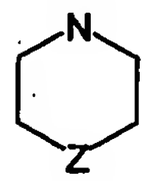
Further R^{23} and $R^{23'}$, independently, may also represent alkyl and alkenyl, at least one of the alkyl and alkenyl carbon atoms, respectively, being replaced by any of O, N and S, for example, methoxymethylen, methoxyethylen, methoxypropylen, ethoxypropylen and the like.

R^{23} and $R^{23'}$ together may also form a heterocyclic ring structure bonded to the side chain via the nitrogen atom in the side chain, the nitrogen atom being linked to the C^{20} carbon atom of the steroid skeleton via the spacer group A. This heterocyclic ring structure, formed by $N(R^{23})(R^{23'})$, may especially be a molety being selected from the group, comprising piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, pyrrolidin-1-yl, pyrrol-1-yl, indol-1-yl, pyrazol-1-yl, imidazol-1-yl, thiazolidin-1-yl and oxazolidin-3-yl ring structures and substituted derivatives thereof. Especially preferred heterocyclic ring structures are the saturated radicals, namely piperidin-1-yl, morpholin-4-yl, piperazin-1-yl and pyrrolidin-1-yl. The heterocyclic ring structures may be substituted with hydroxy, carboxy, amino, alkylamino, dialkylamino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkylcycloalkyl, aryl, alkylaryl, hydroxy, alkoxy, alkylcycloalkyloxy, alkyloxycycloalkyl, alkylaryloxy, alkyloxyaryl, halogen and acyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkoxy and acyl have a number of carbon atoms as indicated above. The heterocyclic ring structure may also be substituted with heterocyclic radicals, such as the heterocyclic ring structures to which they may be bonded and in addition to these as the further radicals, for example, pyridinyl, chinolinyl, isochinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, chinoxalinyl, thiazolyl and oxazolyl, further including all other isomers of these

radicals, for example, pyridin-2-yl, pyridin-3-yl and pyridin-4-yl. Further if $N(R^{23})(R^{23'})$ is a heterocyclic ring structure this ring structure may also include an oxo group in the ring.

If $N(R^{23})(R^{23'})$ is piperazin-1-yl this moiety may be especially substituted by pyridin-2-yl, pyridin-3-yl and pyridin-4-yl, to preferably give the respective $N(R^{23})(R^{23'})$ groups in which the piperazin-1-yl group is substituted in *para*-position, for example, 4-(pyridin-3-yl)piperazin-1-yl.

$N(R^{23})(R^{23'})$ may also be any moiety shown of the following formula:



bonded to C^{20} in the side chain of the steroid skeleton via the nitrogen atom of this moiety, wherein Z = O, S, N-R^{24}, N-C(O)-R^{24}, wherein R^{24} is alkyl, alkenyl, alkynyl, aryl, the number of carbon atoms of which is defined as above. Further R^{24} may be a heterocyclic ring structure, wherein the number of ring atoms is as defined above.

The nitrogen atom of $N(R^{23})(R^{23'})$ is not bonded directly but via A to the C^{20} atom, wherein A is an unsubstituted or substituted methylen or ethylen spacer group, such as for example, (unsubstituted) methylen and (unsubstituted) ethylen and further *iso*-propylen, *tert*-butylen and the like. Preferably A is methylen and ethylen.

Especially preferable are compounds, in which R^3 is hydroxy or hemi succinate ester, in which R^4, $R^{4'}$ and R^{20} are each methyl and in which the heterocyclic ring structure $N(R^{23})R^{23'})$ including the amino nitrogen atom is an unsubstituted or substituted morpholin-4-yl, piperidin-1-yl, piperazin-1- or pyrrolidin-1-yl. $N(R^{23})(R^{23'})$ is in particular 3-hydroxypiperidin-1-yl, 4-hydroxy-piperidin-1-yl, 3-ketopiperidin-1-yl, 4-ketopiperidin-1-yl, 4-dimethylamino-piperidin-1-yl, 3,3-dimethylpiperidin-1-yl, 4,4-dimethylpiperidin-1-yl, 3-carboxypiperidin-1-yl, 4-carboxy-piperidin, 4-phenylpiperidin-1-yl, 4-benzoyl-piperidin-1-yl, 4-(piperidin-1-yl)-piperidin-1-yl, 4-methylpiperazin-1-yl, 4-acetylpiperazin-1-yl, 4-phenylpiperazin-1-yl, 4-benzylpiperazin-1-yl, 4-benzoylpiperazin-1-yl, 4-(pyridin-2-yl)piperazin-1-yl, 4-(pyridin-4-yl)-piperazin-1-yl, 4-(pyrimidin-2-yl)piperazin-1-yl.

Hydrogen atoms may be bonded to all other skeleton C atoms of the steroid compounds, i.e. to C^1, C^2, C^6, C^7, C^8, C^9, C^{11}, C^{12}, C^{14}, C^{15} and C^{16}.

Preferably pharmaceutically acceptable compounds of the present invention are salts of steroid compounds of general formula **X**. Examples of these salts are listed in *Journal of Pharmaceutical Science*, 66, 2 et seq. (1977), which are hereby incorporated by reference. Examples of such salts include salts of organic acids such as formic acid, fumaric acid,

acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, succinic acid, malic acid, tartaric acid, citric acid, benzoic acid, salicylic acid, methane sulphonic acid and the like. Suitable inorganic acids to form pharmaceutically acceptable salts include hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and the like.

The use of the following compounds according to the present invention is especially preferred:

1) (20S)-20-[(3,3-dimethylpiperidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol;
2) (20S)-20-[(piperidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol;
3) (20S)-20-[(4,4-dimethylpiperidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol;
4) (20S)-20-[(4-methylpiperazin-1-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol;
5) (20S)-20-[(4-phenylpiperazin-1-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol;
6) (20S)-20-[(morpholin-4-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol;
7) (20S)-20-[(4-(pyrimidin-2-yl)piperazin-1-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol;
8) (20S)-20-[(pyrrolidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol;
9) (20S)-20-[(3,3-dimethylpiperidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol hemisuccinate;
10) (20S)-20-[N-(3-methoxypropyl)aminomethyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol;
11) (20S)-20-aminomethyl-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol;
12) (20S)-20-[N,N-di-(2-methoxyethyl)aminomethyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol;
13) (20S)-20-[N-(2,2-dimethylethylen)aminomethyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol;
14) (20S)-20-[(piperidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-5,7-dien-3β-ol;
15) (20S)-20-[(4-(pyridin-2-yl)piperazin-1-yl)ethyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol;
16) (20S)-20-[(4-phenylpiperazin-1-yl)ethyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol;
17) (20S)-20-[(4-methylpiperazin-1-yl)ethyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol;
18) (20S)-20-[(N,N-dimethylamino)ethyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol;
19) (20S)-20-[(morpholin-4-yl)ethyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol;
20) (20S)-20-[(pyrrolidin-1-yl)ethyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol;
21) (20S)-20-[(piperidin-1-yl)ethyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol;
22) (20S)-20-[(4-phenylpiperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol;
23) (20S)-20-[(piperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol;
24) (20S)-20-[(morpholin-4-yl)methyl]-5α-pregna-5-en-3β-ol;
25) (20S)-20-[(pyrrolidin-1-yl)methyl]-5α-pregna-5-en-3β-ol;
26) (20S)-20-[(4-carboxyethylpiperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol;

27) (20S)-20-[(3-hydroxypiperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol;

28) (20S)-20-[(4-benzoylpiperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol;

29) (20S)-20-[(4-(piperidin-1-yl)piperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol;

30) (20S)-20-[(4-thiomorpholinyl)methyl]-5α-pregna-5-en-3β-ol;

31) (20S)-20-[(4-dimethylaminopiperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol;

32) (20S)-20-[(4-ketopiperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol;

33) (20S)-20-[(3-ketopiperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol;

34) (20S)-20-[(4-carboxylpiperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol;

35) (20S)-20-[(3-carboxylpiperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol;

36) (20S)-20-[(4-hydroxypiperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol;

37) (20S)-20-[(3,3-dimethylpiperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol;

38) (20S)-20-[(4,4-dimethylpiperidin-1-yl)methyl]-5α-pregna-5α-en-3β-ol;

39) (20S)-20-[(4-piperazin-1-yl)methyl]-5α-pregna-5-en-3β-ol;

40) (20S)-20-[(4-phenylpiperazin-1-yl)methyl]-5α-pregna-5-en-3β-ol;

41) (20S)-20-[(4-methylpiperazin-1-yl)methyl]-5α-pregna-5-en-3β-ol;

42) (20S)-20-[(4-benzylpiperazin-1-yl)methyl]-5α-pregna-5-en-3β-ol;

43) (20S)-20-[(4-acetylpiperazin-1-yl)methyl]-5α-pregna-5-en-3β-ol;

44) (20S)-20-[(4-benzoylpiperazin-1-yl)methyl]-5α-pregna-5-en-3β-ol;

45) (20S)-20-[{4-(2-pyridyl)piperazin-1-yl}methyl]-5α-pregna-5-en-3β-ol;

46) (20S)-20-[{4-(3-pyridyl)piperazin-1-yl}methyl]-5α-pregna-5-en-3β-ol;

47) (20S)-20-[{4-(4-pyridyl)piperazin-1-yl}methyl]-5α-pregna-5-en-3β-ol;

48) (20S)-20-[{4-(2-pyrimidyl)piperazin-1-yl}methyl]-5α-pregna-5-en-3β-ol;

49) (20S)-20-[(piperidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-$\Delta^{8(14)}$-en-3β-ol;

50) (20S)-20-[(piperidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-5-en-3β-ol;

51) (20S)-20-[(morpholin-4-yl)methyl]-4,4-dimethyl-5α-pregna-5-en-3β-ol;

52) (20S)-20-[(thiomorpholin-4-yl)methyl]-4,4-dimethyl-5α-pregna-5-en-3β-ol;

53) (20S)-20-[(4-methylpiperidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-5-en-3β-ol;

54) (20S)-20-[(3-methylpiperidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-5-en-3β-ol;

55) (20S)-20-[(4-(pyrimidin-2-yl)piperazin-1-yl)methyl]-4,4-dimethyl-5α-pregna-5-en-3β-ol;

56) (20S)-20-[(4-hydroxypiperidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-5-en-3β-ol;

57) (20S)-20-[(3-hydroxymethylpiperidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-5-en-3β-ol;

58) (20S)-20-[(4-methylpiperazin-1-yl)methyl]-5α-pregna-8,14-dien-3β-ol;

59) (20S)-20-[(3-methylpiperidin-1-yl)methyl]-5α-pregna-$\Delta^{8(14)}$-en-3β-ol;

60) (20S)-20-[(3-pyrrolin-1-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol;

61) (20S)-20-[(thiomorpholin-4-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol; and

62) 4,4-dimethyl-5α-cholesta-8,14,24-triene-3β-ol.

The structural formulae of compounds nos. 1-49 are shown in Fig. 1A - Fig. 1K in WO 02/079220 which was published after the priority date of this application.

A further object of the present invention is pharmaceutical compositions comprising at least one MAS compound and at least one pharmaceutically acceptable excipient well known in the art, for example, at least one carrier, diluent, absorption enhancer, preservative, buffer, agent for adjusting the osmotic pressure and rheology of the medicament if it will be liquid, surfactant, solvent, tablet disintegrating agent, micro capsules, filler, slip additive, colorant, flavour and other ingredient. These substances are conventionally used in the art. The steroid compounds used according to the present invention (i.e. the MAS compounds) are preferably comprised in the pharmaceutical compositions in an effective amount.

Examples for solid carriers are magnesium carbonate, magnesium stearate, dextrin, lactose, sugar, talkum, gelatin, pectin, starch, silica gel, tragacanth, methylcellulose, sodium carboxymethyl cellulose, low melting waxes and cacao butter.

Liquid compositions include sterile solutions, suspensions and emulsions, which may be administered for example, orally by nasal administration or as an ointment. Such liquid compositions may also be suitable for injection or for use in connection with *ex vivo* or *in vivo* application. For oral administration the liquid may contain a pharmaceutically acceptable oil and/or lipophilic, surfactant and/or solvent which is miscible with water. In this connection reference is made to WO 97/21440 A1, which is hereby incorporated by reference.

Liquid compositions may also contain other ingredients, which are conventionally used in the art, some of which are mentioned in the list above. Further a composition for transdermal administration of a compound of the present invention may be provided in the form of a patch. A composition for nasal administration may be provided in the form of a nasal spray in liquid or in powder form.

In order to enhance bioavailability of the steroid compound these compounds may also be formulated as cyclodextrin chlatrates. For this purpose the compounds are compounded with α-, β- or γ-cyclodextrin or derivatives thereof.

Salves, ointments, lotions and other liquids to be administered externally must be in a condition such that the steroid compounds of the present invention may be delivered to the subject in need of regulation of meiosis in sufficient quantity. For this purpose the medicament contains excipients for regulating the rheology of the medicament, surfactants, pre-

servatives, solvents, diluents, substances for enhancing skin permeation ability, further flavours and protective skin substances such as conditioners and moisture regulators.

The medicament may also contain further active agents to enhance or regulate the effectiveness of the steroid compounds or to produce other desired effects of the medicament.

For parenteral administration the steroid compounds (i.e., the MAS compounds) may be dissolved or suspended in a pharmaceutically acceptable diluent. Oils are very often used in combination with solvents, surfactants, suspension or emulsion agents, for example, olive oil, peanut oil, soybean oil, caster oil and the like. For the preparation of an injectable medicament any liquid carrier may be employed. These liquids often also contain agents for the regulation of the viscosity thereof as well as agents for regulating isotonicity of the liquid.

The steroid compound according to the present invention may further be administered as an injectable depot or as an implantate, which may for example, be administered subcutanely, such that delayed release of the steroid compounds is made possible. For this purpose various techniques may be employed, for example, administration of depots, which include a membrane containing the active compound, or of slowly dissolving depots. Implantates may, for example, contain biologically degradable polymers or synthetic silicones as inert material.

The dose of a steroid compound to be used will be determined by a physician and will depend *inter alia* on the particular steroid compound employed, on the route of administration and on the purpose of the use. In general, the compositions of the present invention are prepared by intimately bringing into association the active compound with the liquid or solid auxiliary ingredients and then, if necessary, shaping the product into the desired formulation.

Usually not more than 3000 mg, preferably not more than 350 mg, and in some preferred instances not more than 30 mg of the steroid compounds are to be administered to mammals, for example, to humans, per day.

The present invention also relates to the use of the steroid compounds for the preparation of a composition useful according to this invention. Preferably this composition is applicable as a medicament.

The route of administration of compositions containing a compound of the present invention may be any route, which effectively transports the active steroid compound to its site of action.

Thus, when the steroid compounds are to be administered to a mammal, they are conveniently provided in the form of a pharmaceutical composition, which comprises at least

one steroid compound according to the present invention in connection with a pharmaceutically acceptable carrier. For oral use, such compositions are preferably in the form of tablets or capsules.

The aforementioned steroid compounds can be synthesised analogously with the preparation of known compounds, vide, for example, WO 02/079220.

PHARMACOLOGICAL METHODS

Female Wistar rats were treated one time with ZK 255884 (80 mg/kg s.c.) and serum samples obtained the following days. After an alkaline hydrolysis, neutrals sterols were extracted in cyclohexane. Trimethylsilyl (herein designated TMS) derivatives of the sterols were generated and measured by gas-chromatography/mass-spectrometry.

For cell culture experiments, HepG2 cells were incubated with different concentrations of ZK 255884 for 24 hours. After extraction and an alkaline hydrolysis, neutral sterols were converted to their TMS-derivatives and measured by gas-chromatography/mass-spectrometry.

The drawing below with the heading "Influence on ZK 255884 on serum sterols in rats" (Fig. 1a & 1b) shows than there is a cholesterol peak (designated Ch.) in the control group (Fig. 1a)) and, apparently no desmosterol peak, whereas, in Fig. 1b, by administering once 80 mg/kg of ZK 255884, the cholesterol level is decreased and the desmosterol level is increased substantially. This indicates an interference in the cholesterol synthesis at the desmosterol → cholesterol step.

Fig. 2 with the heading "Influence on ZK 255884 on serum sterols in rats" shows than by administering once 80 mg/kg of ZK 255884, after 4 days, the cholesterol level is decreased from about 65 to about 10, whereas the control is only decreased to about 40 (left figure). The right figure shows that for both the control and for ZK 255884, the amount of total sterol (defined as cholesterol + desmosterol) is approximately the same at the various times.

The left figure on Fig. 3 with the heading "Influence on ZK 255884 on serum sterols in rats" shows than by administering once 80 mg/kg of ZK 255884 the desmosterol level increases

over time and only tend to decrease on day 5, which is also true for the ratio of desmosterol to cholesterol, given on the right figure on Fig. 3.

Figs. 4a, 4b, 4c, and 4d with the heading "Influence on ZK 255884 on sterols in Hep G2 cells" shows a dose response curve to increase desmosterol and the appearance of another sterol at the highest concentrations of 10 µMin this human liver cell line.

Fig. 5 with the heading "Influence on ZK 255884 on cholesterol synthesis in Hep G2 cells" shows a dose response curve in increasing the ratio of desmosterol to cholesterol. The decline of the ratio of desmosterol to cholesterol at the highest concentration (10 µM) is probably due to the additional appearance of another sterol, probably another cholesterol precursor (for example, zymosterol).

CLAIMS

1. Use of a compound of the general formula X stated above with the definitions stated above or FF-MAS for increasing the HDL cholesterol to non-HDL cholesterol ratio.

2. Use of a compound of the general formula X stated above with the definitions stated above or FF-MAS for treatment and/or prevention of artherosclerosis.

3. Use of a compound of the general formula X stated above with the definitions stated above or FF-MAS for treatment and/or prevention of hyperlipidemia.

4. Use of a compound of the general formula X stated above with the definitions stated above or FF-MAS for treatment of diabetic dyslipididemia.

5. Use of a compound of the general formula X stated above with the definitions stated above or FF-MAS for treatment of hyper-cholesterolemia.

6. Use of a compound of the general formula X stated above with the definitions stated above or FF-MAS for treatment of diseases of illness related to metabolic dysfunction.

7. Use of a compound of the general formula X stated above with the definitions stated above or FF-MAS for treatment of obesity or obesitas related diseases or as an appetite regulator.

8. Use of a compound of the general formula X stated above with the definitions stated above or FF-MAS for treatment of neurological diseases.

9. The use according to any of the preceding claims wherein the compound of formula X is (20S)-20-[(3,3-dimethylpiperidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol; (20S)-20-[(piperidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol; (20S)-20-[(4,4-dimethylpiperidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol; (20S)-20-[(4-methylpiperazin-1-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol; (20S)-20-[(4-phenylpiperazin-1-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol; (20S)-20-[(morpholin-4-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol; (20S)-20-[(4-(pyrimidin-2-yl)piperazin-1-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol; (20S)-20-[(pyrrolidin-

1-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol; (20S)-20-[(3,3-dimethylpiperidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol hemisuccinate; (20S)-20-[N-(3-methoxypropyl)aminomethyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol; (20S)-20-amino-methyl-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol; (20S)-20-[N,N-di-(2-methoxyethyl)amino-methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol; (20S)-20-[N-(2,2-dimethylethylen)amino-methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol; (20S)-20-[(piperidin-1-yl)methyl]-4,4-di-methyl-5α-pregna-5,7-dien-3β-ol; (20S)-20-[(4-(pyridin-2-yl)piperazin-1-yl)ethyl]-4,4-di-methyl-5α-pregna-8,14-dien-3β-ol; (20S)-20-[(4-phenylpiperazin-1-yl)ethyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol; (20S)-20-[(4-methylpiperazin-1-yl)ethyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol; (20S)-20-[(N,N-dimethylamino)ethyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol; (20S)-20-[(morpholin-4-yl)ethyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol; (20S)-20-[(pyrrolidin-1-yl)ethyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol; (20S)-20-[(piperidin-1-yl)ethyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol; (20S)-20-[(4-phenyl-piperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[(piperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[(morpholin-4-yl)methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[(pyrrolidin-1-yl)methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[(4-carboxyethylpiperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[(3-hydroxypiperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[(4-benzoylpiperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[(4-(piperidin-1-yl)piperidin-1-yl)methyl]5α-pregna5-en-3β-ol; (20S)-20-[(4-thiomorpholinyl)methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[(4-dimethylaminopiperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[(4-ketopiperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[(3-keto-piperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[(4-carboxylpiperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[(3-carboxylpiperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[(4-hydroxypiperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[(3,3-dimethyl-piperidin-1-yl)methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[(4,4-dimethylpiperidin-1-yl)methyl]-5α-pregna-5α-en-3β-ol; (20S)-20-[(4-piperazin-1-yl)methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[(4-phenylpiperazin-1-yl)methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[(4-methylpiperazin-1-yl)methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[(4-benzylpiperazin-1-yl)methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[(4-acetylpiperazin-1-yl)methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[(4-benzoylpiperazin-1-yl)methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[{4-(2-pyridyl)piperazin-1-yl}methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[{4-(3-pyridyl)piperazin-1-yl}methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[{4-(4-pyridyl)piperazin-1-yl}methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[{4-(2-pyrimidyl)piperazin-1-yl}methyl]-5α-pregna-5-en-3β-ol; (20S)-20-[(piperidin-1-yl)-methyl]-4,4-dimethyl-5α-pregna-$\Delta^{8(14)}$-en-3β-ol; (20S)-20-[(piperidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-5-en-3β-ol; (20S)-20-[(morpholin-4-yl)methyl]-4,4-dimethyl-5α-

pregna-5-en-3β-ol; (20S)-20-[(thiomorpholin-4-yl)methyl]-4,4-dimethyl-5α-pregna-5-en-3β-ol; (20S)-20-[(4-methylpiperidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-5-en-3β-ol; (20S)-20-[(3-methylpiperidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-5-en-3β-ol; (20S)-20-[(4-(pyrimidin-2-yl)piperazin-1-yl)methyl]-4,4-dimethyl-5α-pregna-5-en-3β-ol; (20S)-20-[(4-hydroxypiperidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-5-en-3β-ol; (20S)-20-[(3-hydroxymethylpiperidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-5-en-3β-ol; (20S)-20-[(4-methylpiperazin-1-yl)methyl]-5α-pregna-8,14-dien-3β-ol; (20S)-20-[(3-methylpiperidin-1-yl)-methyl]-5α-pregna-$\Delta^{8(14)}$-en-3β-ol; (20S)-20-[(3-pyrrolin-1-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol; (20S)-20-[(thiomorpholin-4-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol; and 4,4-dimethyl-5α-cholesta-8,14,24-triene-3β-ol.

10. Use of a sterol Δ^{24} reduktase inhibitor to treat or prevent any of the following diseases: artherosclerosis, hyperlipidemia, dyslipididemia, for example diabetic dyslipididemia, hyper-cholesterolemia, diseases of illness related to metabolic dysfunction, obesity, obesitas related diseases, neurological diseases, for example, Alzheimer disease.

11. Any novel feature or combination of features.

Novo Nordisk A/S & Schering Aktiengesellschaft

Influence of ZK 255884 on serum sterols in rats

Animals: female Wistar rats (approx. 200 g) Cycle: start at met-estrus Treatment: one time ZK 255884; 80 mg/kg s.c. on d1

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RIC
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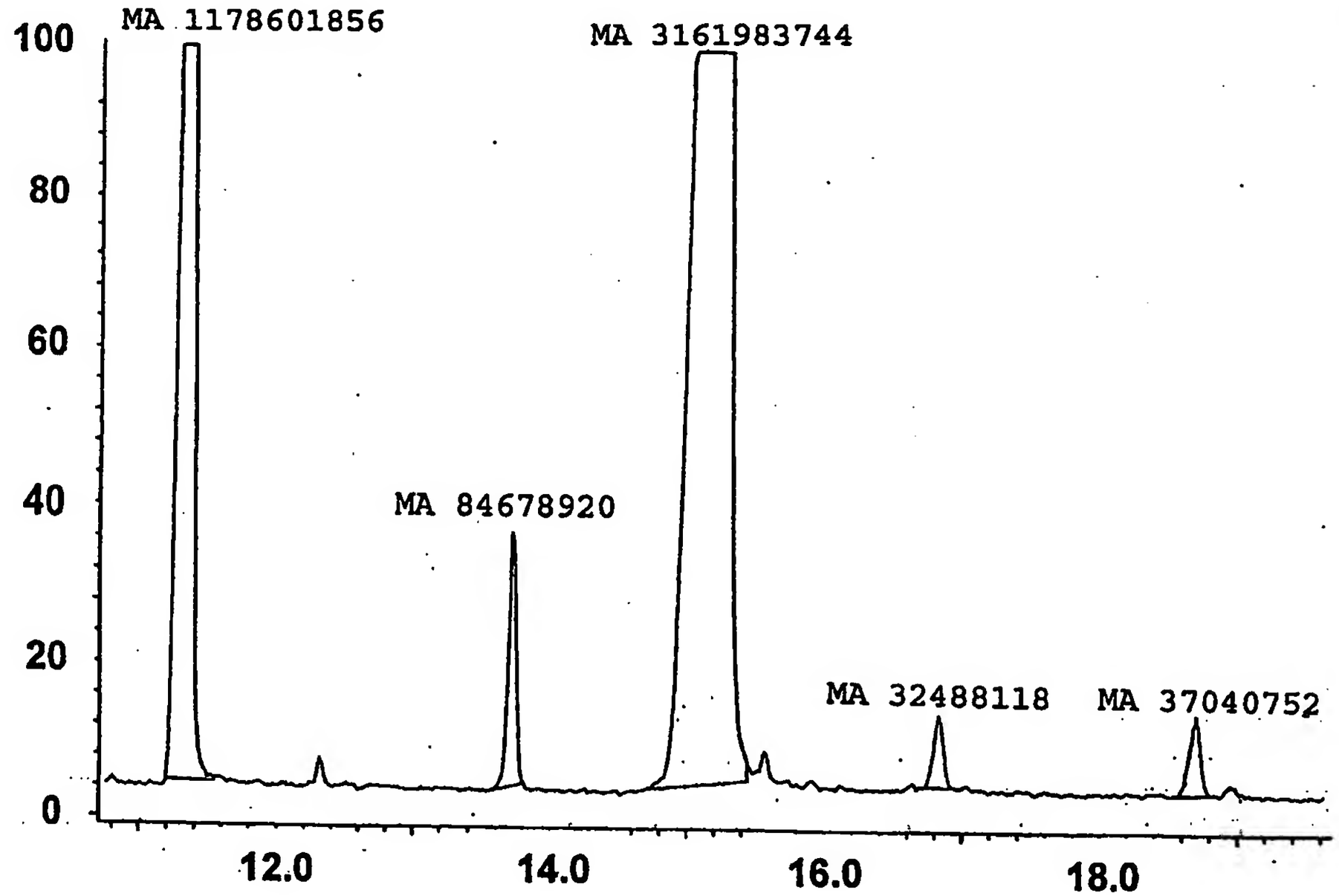


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Times:    0.3>24.0

Inlet:    GC  Vial:22
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Masses:   49 > 550
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              6.9E+07
              x4
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Date: Fri Jun 14 16:46:31 2002 ICIS: 8.3.0 SP2 for OSF1 (v4.0) build 98-238 from 26-Aug-98

Fig. 1a

Influence of ZK 255884 on serum sterols in rats (continued)

Animals: female Wistar rats (approx. 200 g) Cycle: start at met-estrus Treatment: one time ZK 255884; 80 mg/kg s.c. on d1

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Oper:  Hi                                   Study:  TSQ700
Peak:  1000.0 mmu                           RIC: 200572331
Area:  2,  4,   0                 Baseline:   20, 3

Elapse:    1  9  0.26
Times:     0.3>24.0

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                x4
RIC
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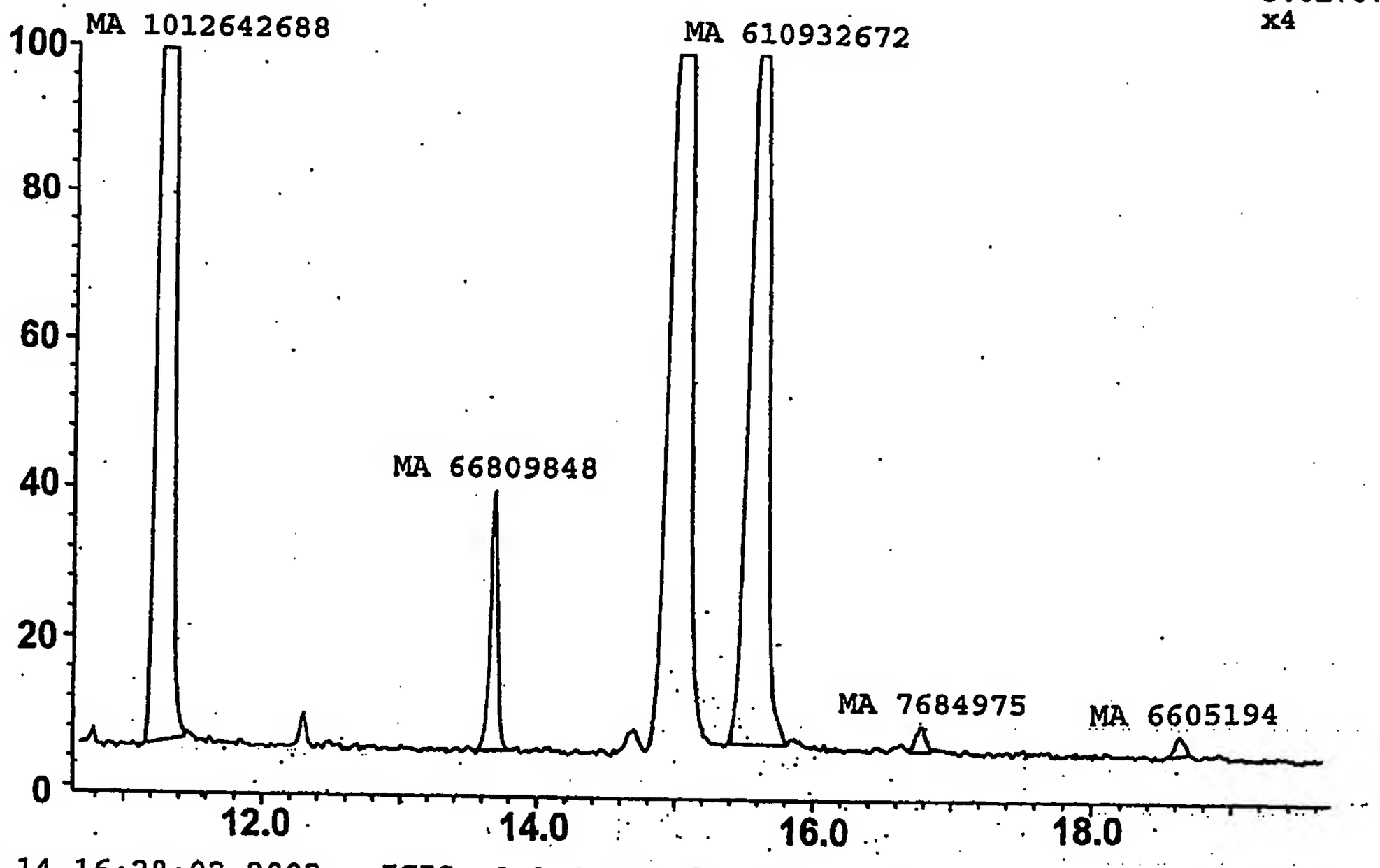


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Fig. 1b

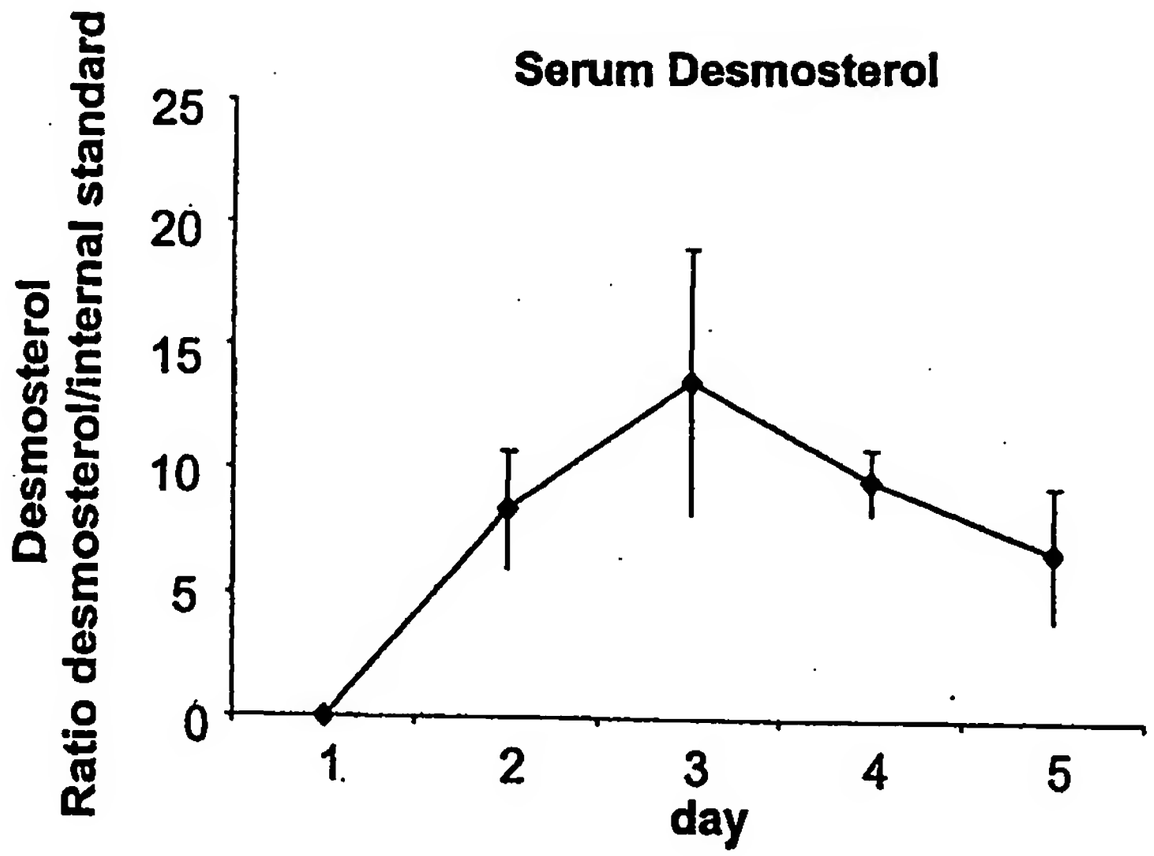
PCT/DK2003/000619

Influence of ZK 255884 on serum sterols in rats
Animals: female Wistar rats (approx. 200 g)
Cycle: start at met-estrus
Treatment: one time ZK 255884; 80 mg/kg s.c. on d1
Serum Cholesterol
Cholesterol
Ratio cholesterol/internal standard
day
Total stero
Cholesterol + Desmosterol
day
◆ Vehicel
■ ZK 255884

Fig. 2

Influence of ZK 255884 on serum sterols in rats

Animals: female Wistar rats (approx. 200 g)
Cycle: start at met-estrus
Treatment: one time ZK 255884; 80 mg/kg s.c. on d1



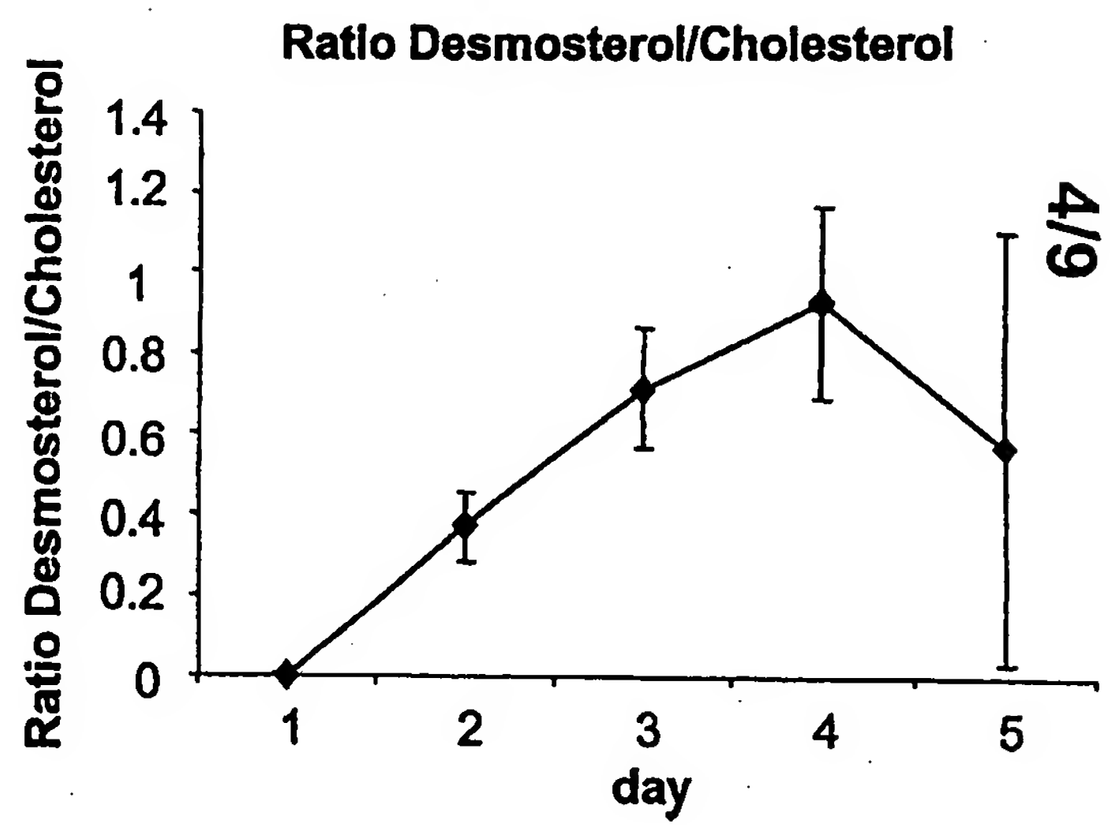


Fig. 3

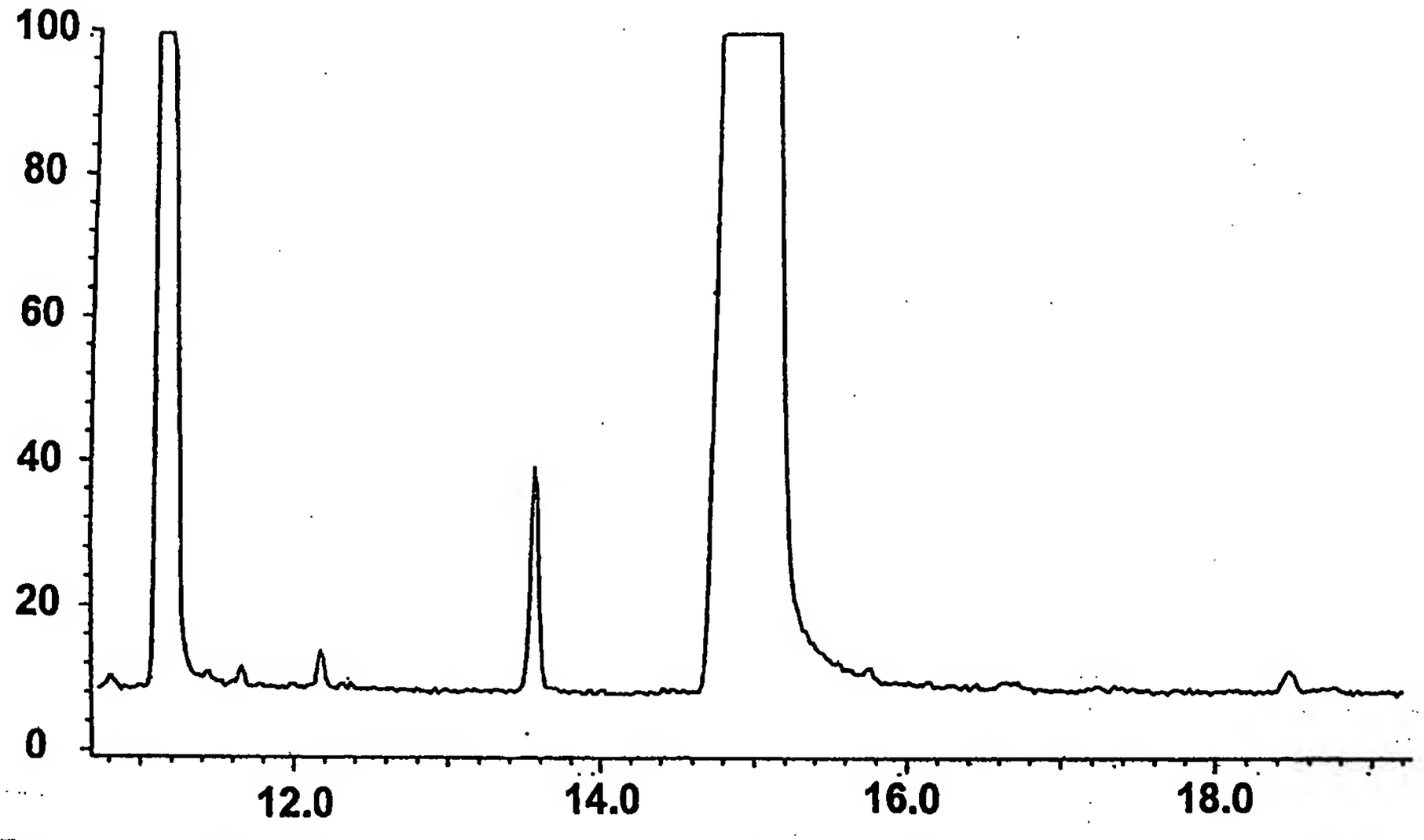
Influence of ZK 255884 on sterols in Hep G2 cells

Incubation for 24 h at different concentrations of ZK 255884

```
CHRO:   G255884k2.dat (29-MAY-02 02:56:47)
Samp:   255884-8
Comm:   30m HP-1MS (0.25/0.25) 150(1)-20-260-10-280(15) 100 kPa
Mode:   EI +Q3MS LMR UP LR
Oper:   Hi                                  Study:  TSQ700
Peak:   1000.0 mmu                          RIC:  397076134

RIC                                                          Elapse:      1 9 0.26
                                                             Times:      0.3 > 24.0

                                                             Inlet:      GC  Vial: 33
                                                             Client:     Lindenthal
                                                             Masses:     49 > 550
                                                                          9.9E+07
                                                                          x4
```

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Date: Fri Jun 14 17:44:14 2002  ICIS: 8.3.0 SP2 for OSF1 (v4.0) build 98-238 from 26-Aug-98
```

Fig. 4a

Influence of ZK 255884 on sterols in Hep G2 cells (continued)

Incubation for 24 h at different concentrations of ZK 255884

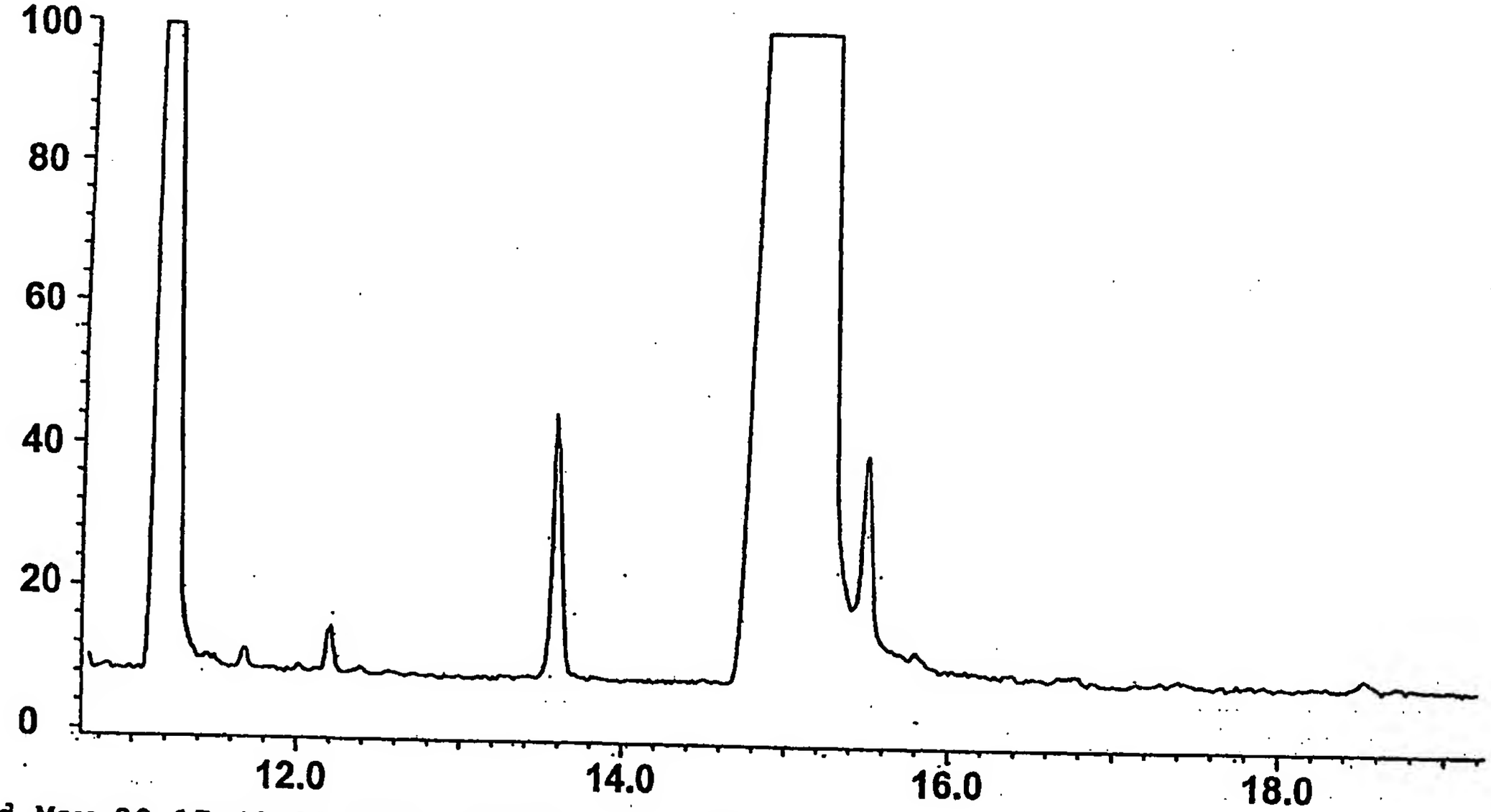
CHRO: G255884h1.dat (29-MAY-02 00:03:23)
Samp: 255884-8
Comm: 30m HP-1MS (0.25/0.25) 150(1)-20-260-10-280(15) 100 kPa
Mode: EI +Q3MS LMR UP LR
Oper: Hi
Peak: 1000.0 mmu

Study: TSQ700
RIC: 528094821

Elapse: 1 9 0.26
Times: 0.3 > 24.0

Inlet: GC Vial: 26
Client: Lindenthal
Masses: 49 > 550
1.3E+08
x4

RIC



Date: Wed May 29 17:42:29 2002 ICIS: 8.3.0 SP2 for OSF1 (v4.0) build 98-238 from 26-Aug-98

Fig. 4b

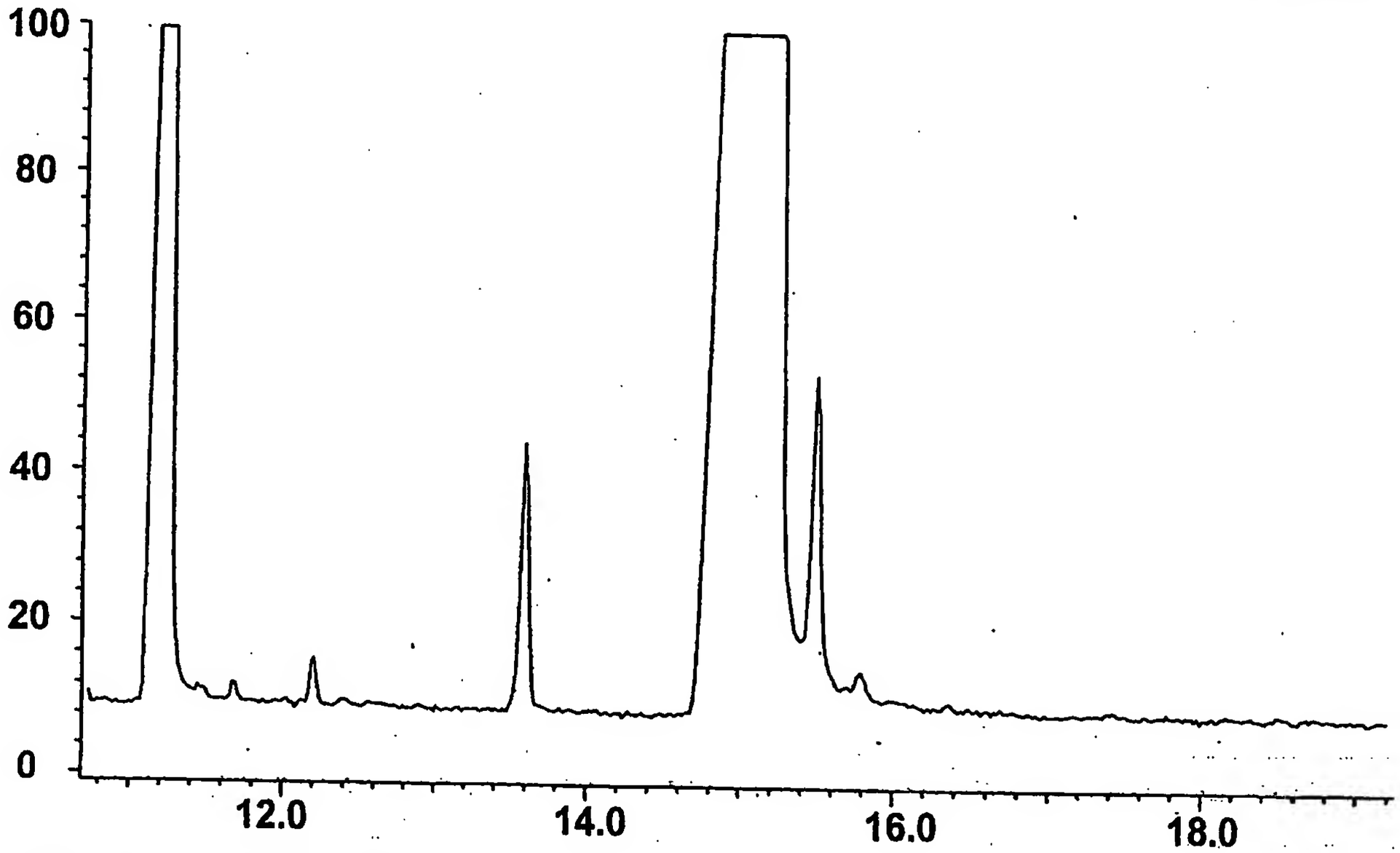
Influence of ZK 255884 on sterols in Hep G2 cells (continued)

Incubation for 24 h at different concentrations of ZK 255884

```
CHRO:    G255884f1.dat (28-MAY-02 22:36:40)
Samp:    255884-3b
Comm:    30m HP-1MS (0.25/0.25) 150(1)-20-260-10-280(15) 100 kPa
Mode:    EI +Q3MS LMR UP LR
Oper:    Hi
Peak:    1000.0 mmu
                                   Study:  TSQ700
                                   RIC:  552849557

Elapse:     1 9 0.26
Times:     0.3 > 24.0

Inlet:     GC  Vial: 22
Client:    Lindenthal
Masses:    49 > 550
                1.4E+08
                x4
```



Date: Wed May 29 17:40:56 2002 ICIS: 8.3.0 SP2 for OSF1 (v4.0) build 98-238 from 26-Aug-98

Fig. 4c

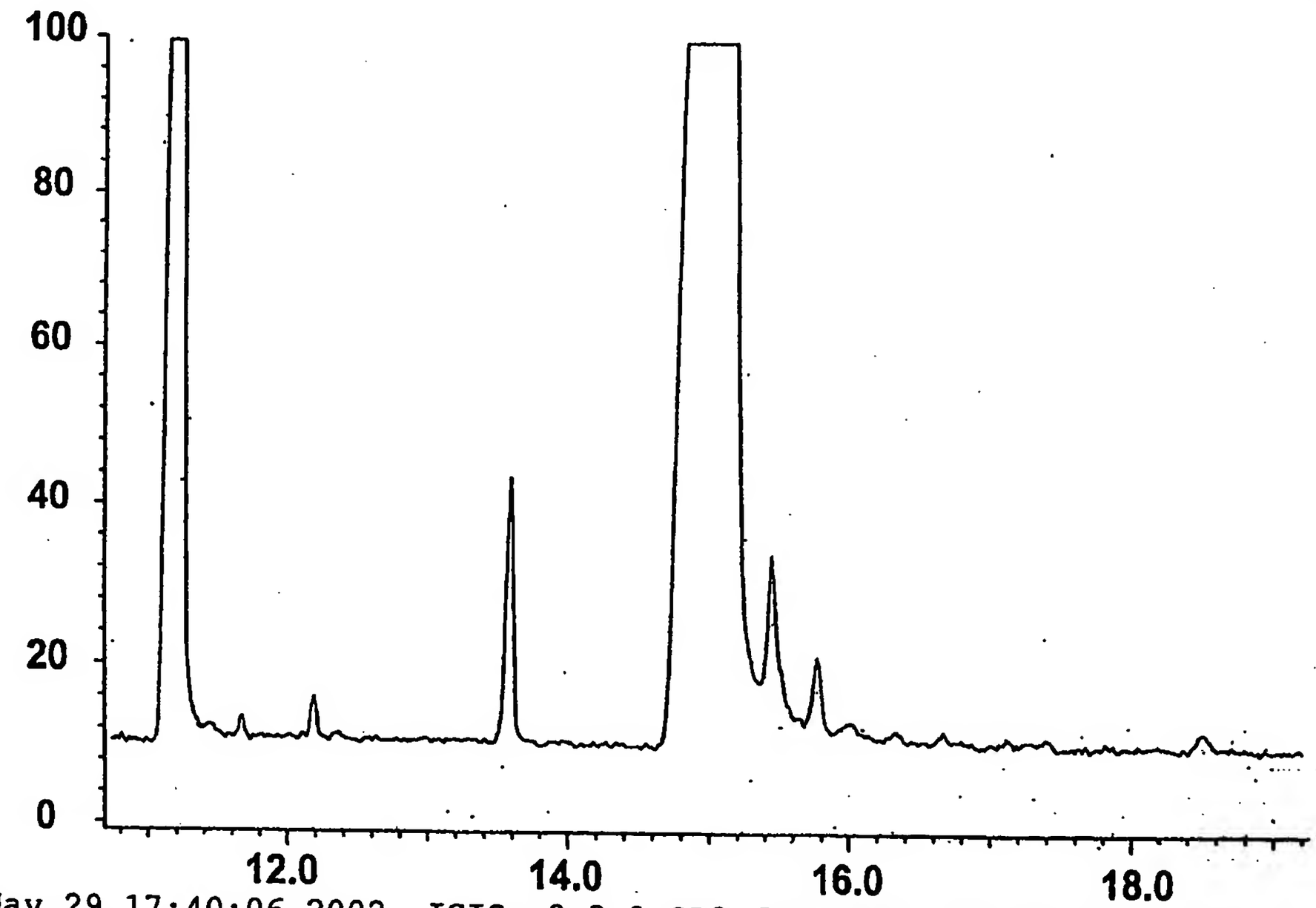
Influence of ZK 255884 on sterols in Hep G2 cells (continued)

Incubation for 24 h at different concentrations of ZK 255884

```
CHRO:    G255884e1.dat (28-MAY-02 21:38:47)
Samp:    255884-3b
Comm:    30m HP-1MS (0.25/0.25) 150(1)-20-260-10-280(15) 100 kPa
Mode:    EI +Q3MS LMR UP LR
Oper:    Hi                                  Study:  TSQ700
Peak:    1000.0 mmu                          RIC:  541667456

Elapse:     1 9 0.26
Times:      0.3 > 24.0

Inlet:      GC  Vial: 20
Client:     Lindenthal
Masses:     49 > 550
                1.4E+08
                x4
```

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Date: Wed May 29 17:40:06 2002  ICIS: 8.3.0 SP2 for OSF1 (v4.0) build 98-238 from 26-Aug-98
```

Fig. 4d

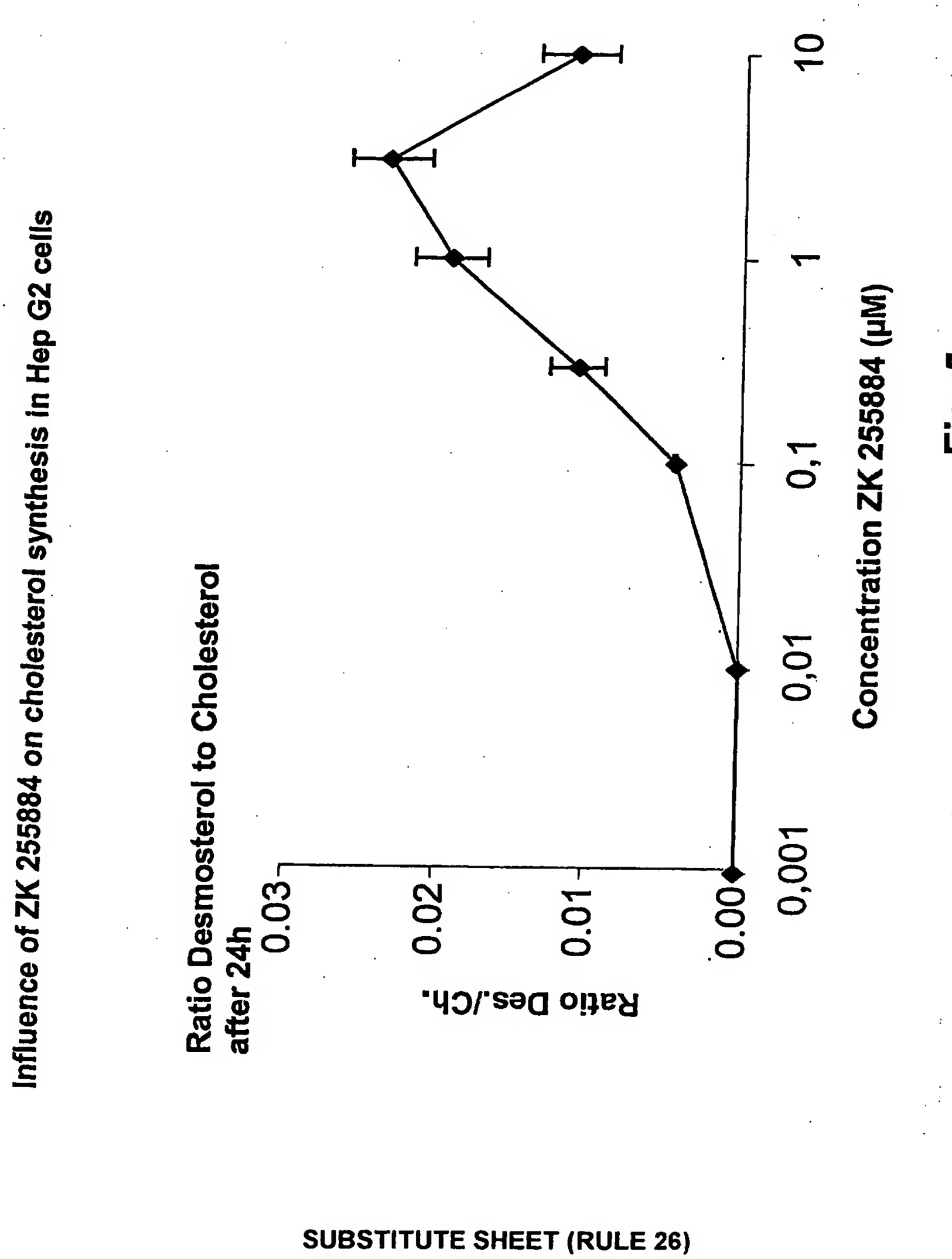
Influence of ZK 255884 on cholesterol synthesis in Hep G2 cells
Ratio Desmosterol to Cholesterol after 24h
Ratio Des./Ch.
0.03
0.02
0.01
0.00
0,001
0,01
0,1
1
10
Concentration ZK 255884 (µM)

Fig. 5

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 03/00619

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/57 A61K31/575 A61K31/58 A61P3/06 A61P9/10
A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 90 03171 A (UNIV NEW YORK) 5 April 1990 (1990-04-05) page 17, line 21 - line 27 ---	1-9
X	US 5 506 354 A (MCCALL JOHN M ET AL) 9 April 1996 (1996-04-09) Ex.E, column 71 and Ey3, column 51 --- -/--	1-9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 January 2004	30. 01. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	ANNA SJÖLUND /EÖ

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 03/00619

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE STN INTERNATIONAL [Online] File HCAPLUS, HCAPLUS accession no. 1992:476542, Document no. 117:76542; MIZUKAMI, JUICHI ET AL: "Phytosterol-containing fat emulsions for injections" XP002267084 see CASRN 17605-67-3 abstract & JP 04 091026 A 24 March 1992 (1992-03-24) ---	1-9
X	CARLOS FERNÁNDEZ ET AL: "Inhibition of cholesterol biosynthesis by 22-unsaturated phytosterols via competitive inhibition of sterol 24-reductase in mammalian cells" BIOCHEM. J., vol. 366, 2002, pages 109-119, XP002267082 the whole document ---	1-9
X	MARCUS J. MUSSNER ET AL: "Effects of Phytosterol Ester-Enriched Margarine on Plasma Lipoproteins in Mild to Moderate Hypercholesterolemia Are Related to Basal Cholesterol and Fat Intake" METABOLISM, vol. 51, no. 2, February 2002 (2002-02), pages 189-194, XP002267083 the whole document -----	1-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 03/00619

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 10 relates to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practised on the human or animal body (PCT Rule 39.1(iv)).

2. [X] Claims Nos.: 11
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-9, partly

directed to the use of steroid derivatives according to formula X, (defined in the description) with N-substitution in the side chain, for treating diseases, connected to increasing the HDL cholesterol to non HDL cholesterol-levels.

2. Claims: 1-9, partly

directed to the use of FF-MAS for treating diseases, connected to increasing the HDL cholesterol to non HDL cholesterol-levels.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 11

Claim 11 is not clear and concise, which is required in PCT art. 6

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK 03/00619

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9003171 A	05-04-1990	US 4939134 A	03-07-1990
		AT 98489 T	15-01-1994
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		DE 68911509 T2	31-03-1994
		EP 0393180 A1	24-10-1990
		JP 3501492 T	04-04-1991
		WO 9003171 A1	05-04-1990
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		EP 0238545 A1	30-09-1987
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		CA 1308707 C	13-10-1992
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		IL 79702 A	16-02-1992
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		AU 614418 B2	29-08-1991
		AU 4080789 A	07-12-1989
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